challenge. Applicants have also submitted evidence that efficacy of the SHIV/macaque model reasonably correlates with the human/HIV model. Applicants now include an additional published review article review showing the SHIV/macaque model as the HIV animal model of choice.

The article, Joag, *Primate Models of AIDS, Microbes and Infection*, 2, 2000, 223-229 (copy attached)), discusses and reviews all of the major HIV animal models. Not surprisingly, the SHIV/macaque model is specifically identified as a key HIV animal model. Indeed, Joag writes that virulent strains of the SHIV virus cause disease in several macaque species. These infected macaques lose T-cells after infection and "[h]istological changes in the lymphoid and other tissues *closely resemble those seen in human AIDS.*" (p. 226, emphasis added). Further, like human AIDS patients, macaques infected with SHIV "also develope organ-specific disease, including encephalitis." (*Id.*)

Thus, the rhesus macaque/SHIV model closely resembles the HIV virus in humans. Because as the SHIV model incorporates the HIV-1 viral envelope, it is "*an ideal model* for evaluating gp120-based vaccine strategies and for studies on passive immunization" (p. 226; emphasis added). Indeed, a major reason for this relationship, is that "the virus envelope plays a dominant role in transmission" (p. 226) of the virus. Joag also points out that "SHIV chimeras with different envelope subtypes are likely to be of *crucial importance in testing candidates for use in humans.*" (p. 227; emphasis added). Moreover, in Table II, Joag summarizes the ability of three different animal models to extrapolate to humans. One of the major drawbacks of the HIV-

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1 model is that pathogenesis can be extrapolated to humans only with great care. In the SIV/HIV-2 model, the ability to extrapolate mucosal transmission as well as immune mechanisms suffer similar drawbacks. No such caution is necessary in any aspect of the SHIV model. Moreover, the SHIV/macaque model is given high extrapolation confidence for antigen vaccines such as gp120 — the type of vaccine claimed by the Applicants.

The Examiner can no longer rely on the outdated science of Haynes et al. The review by Joag refutes the Examiner's position that there are no HIV animal models. Indeed, all that the Applicants must show is that "one of ordinary skill in the art would accept the animal tests as being reasonably predictive of utility in humans." (MPEP § 2107.02). Applicants have not met this test. Table II of Joag states that for gp120 vaccine — the antigen used by the Applicants — extrapolation to humans from the SHIV/macaque model can be done "with a high level of confidence." (p. 225) Further, it remains uncontroverted that Applicants' vaccine protected 10 of 12 macaques when challenged with SHIV. Thus, Applicants meet the enablement standard set forth in the MPEP, and the claims are in condition for allowance.

Appellants filed this continuation application on August 12, 1997, nearly three years ago. Applicants received their first Final Office Action on August 10, 1998, and Applicants filed an appeal brief on June 28, 1999. Instead of resolving this matter on the merits, prosecution was reopened and a new rejection was set forth: obviousness-type double patenting, a rejection that could have been made earlier in prosecution and which would have avoided the necessity of appealing to the Board a second time. Applicants obviated the double patenting by filing a

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terminal disclaimer on January 14, 2000. Notwithstanding the PTO's own admission that "it would have been *prima facie* obvious to one of ordinary skill in the art of the time the claimed invention was made to use the claimed vaccines and methods of U.S. Patent No. 5,750,110 and to substitute an HIV antigen in place of other antigens for the expected benefits of obtaining a vaccine for treating or preventing HIV infection," the PTO maintained the enablement rejection. The PTO's enablement and double patenting rejections are logically inconsistent with each other.

Applicants again submit that the present application meets the enablement standard under the patent laws and rules. In conjunction with the present Request for Reconsideration, Applicants submit the article by Joag and file a second notice of appeal and a second appeal brief.

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CONCLUSION

In view of the foregoing remarks, Applicants respectfully request the timely allowance of the pending claims. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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